1.0 Purpose:

To describe the Division of Microbiology and Infectious Diseases (DMID) policy for unblinding individual volunteers in clinical studies or trials.

2.0 Scope:

This policy pertains to DMID staff and study site staff involved in the oversight or conduct of blinded clinical research. This policy does not addresses unblinding required by regulatory agencies nor unblinding in response to immediate hazards to volunteers.

3.0 Policy:

A study volunteer's assignment to an investigational product or intervention in a blinded study may be unblinded to DMID and/or the investigator in the event of specific unexpected medical events. The Principal Investigator (PI) should notify DMID if there is a request to unblind an individual study participant. The DMID Scientific Branch and the Medical Monitor (MM) will make the decision. If necessary, consultation with the investigator, Medical Officer (MO), the Associate Director for Clinical Research, the treating physician, the primary care physician, and the safety oversight committee (SOC) will occur. This policy includes but is not restricted to:

1. An adverse event for which knowing the study assignment is necessary to direct or manage current or future care of the volunteer, interpret the event, or provide critical safety information that could impact the ongoing conduct of the trial.
2. A volunteer becomes pregnant while she is still receiving the investigational product or intervention.
3. A pregnant volunteer or fetus that remains at risk as a result of having received the investigational product or intervention.
4. An unexpected adverse event of a unique nature where knowledge of the assignment may impact decisions on enrollment or continuation.

In any case, if the PI becomes aware of an intentional or unintentional breaking of the blind, they should report the unblinding through the protocol deviation reporting process. The PI should also fully document and explain the reasons for unblinding in the final clinical report.

4.0 Background:

The most important design strategies for avoiding bias in controlled clinical trials are randomization and blinding of study product assignment. Bias may arise from the influence of knowledge of the treatment received. This knowledge may have an effect on the recruitment and allocation of volunteers, their subsequent care, the attitudes of volunteers to the investigational product or interventions, the assessment of end-points, the handling of withdrawals, the exclusion of data from analysis, etc. Blinding reduces or minimizes the occurrence of conscious or unconscious bias in the conduct of and interpretation of results from clinical studies and trials.

DMID's SOCs evaluate unexpected experiences/events to determine whether there may be a potential relationship to the study product or intervention. In most cases, it is not necessary to

unblind the study. However, in rare instances the investigator, DMID MO, MM, or Scientific Branch staff may initiate discussions of unblinding single volunteers outside of the normal SOC review when deemed essential for the care of the volunteer or when knowledge of the assignment may impact others. The SOC may choose to review unblinded data in the closed session of the SOC meeting, but this is outside the scope of this policy.

5.0 Definitions:

Adverse event: Any untoward medical occurrence in a volunteer receiving a study product or intervention whether it is related or not.

Assignment: The study group to which the volunteer is assigned to receive an. investigational product or control or other intervention.

Blinding: A procedure in which one or more parties participating or involved in the study are kept unaware of the treatment assignment(s).

Safety Oversight Committee (SOC): An SOC refers to a committee of experts, independent of the trial investigators, pharmaceutical sponsor (if any) and funding agency, that periodically reviews the conduct and results of the clinical trial. Following review the SOC makes recommendations to: continue without change, continue with change, or terminate the trial. An SOC refers to either a Data and Safety Monitoring Board (DSMB) or a Safety Monitoring Committees (SMC).

Data Safety Monitoring Board (DSMB): A DSMB is an independent group of experts that advises DMID on Phase II randomized multi-center trials, Phase III, or Phase IV trials. It is the responsibility of the DSMB to periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy

Safety Monitoring Committee (SMC): An SMC is a group of independent experts that advise DMID on safety reports from Phase I and some Phase II trials. The responsibility of the SMC is to monitor participant safety.

6.0 Responsibilities:

Role	Responsibility
Scientific Branches	• Discuss with the investigator, MO, MM, and the Associate Director for Clinical Research, as necessary, whether to unblind a volunteer
Medical Monitor or designee	• Discuss with the investigator, Scientific Branches, MO, and the Associate Director for Clinical Research, as necessary, whether to unblind a volunteer
Office of Clinical Research Affairs	• Notify the Scientific Branch and the Associate Director for Clinical Research of events that might lead to unblinding a study volunteer • Authority to effect the release of treatment assignments by working with the appropriate individuals within DMID.
Study Site Staff	• Authority to immediately unblind subjects to remove immediate hazards and provide essential care. For all other situations, unblinding will be done in consultation with DMID

7.0 References:

International Conference on Harmonization (ICH)

E2A: Clinical Safety Data Management: Definitions And Standards For Expedited Reporting

E6 Good Clinical Practice: Consolidated Guidance – Sections 4.7, 5.5.3 (g), 5.13.1, 5.13.4

E9: Statistical Principles for Clinical Trials

Food and Drug Administration Guidance for Industry and Investigators

Safety Reporting Requirements for INDs and BA/BE Studies (draft Guidance)

8.0 Inquiries:

Questions or comments regarding this policy may be directed to:

Associate Director for Clinical Research
Division of Microbiology and Infectious Diseases (DMID)
NIH / NIAID
5601 Fisher Lane, Room 7E60
Bethesda, MD 20892
PolicyQuery@DMID.NIAID.NIH.gov

9.0 Availability:

This policy is located electronically at:
https://www.niaid.nih.gov/sites/default/files/unblindingindividuals.pdf

10.0 Change Summary:

Version number	Date of Revision: DD/MMM/YYYY	Replaces	Effective Date: DD/MMM/YYYY	Description of Revision/Retirement
1.0	N/A	N/A	01/FEB/2013	N/A
2.0	05/MAR/2015	1.0	01/APR/2015	Biennial review; Administrative edits
2.0	10/MAR/2017	N/A	01/APR/2015	Biennial review; no changes